VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at line 14 of page 10 has been amended as follows:

The present invention further provides substantially purified polypeptides comprising the amino acid sequence comprising SEQ ID NOS:[61,] 63, 64, 65, 67, and [68] 69. In another embodiment, the present invention also provides purified, isolated polynucleotide sequences encoding the polypeptides comprising the amino acid sequences of SEQ ID NOS:[61,] 63, 64, 65, 67, [and]68 and 69. The present invention contemplates portions or fragments of SEQ ID NOS:[61,] 63, 64, 65, 67, and [68] 69, of various lengths. In one embodiment, the portion of polypeptide comprises fragments of lengths greater than 10 amino acids. However, the present invention also contemplates polypeptide sequences of various lengths, the sequences of which are included within SEQ ID NOS:[61,] 63, 64, 65, 67, and [68] 69, ranging from 5 to 500 amino acids (as appropriate, based on the length of SEQ ID NOS:[61,] 63, 64, 65, 67, and [68] 69).

The paragraph beginning at line 25 of page 10 has been amended as follows:

The present invention also provides nucleic acid sequences comprising SEQ ID NOS:55, 62, 66, and [69] 68, or variants thereof. The present invention further provides fragments of the isolated polynucleotide sequences that are at least 6 nucleotides, at least 25 nucleotides, at least 30 nucleotides, at least 50 nucleotides, at least 100 nucleotides, at least 250 nucleotides, and at least 500 nucleotides in length (as appropriate for the length of the sequence of SEQ ID NOS:55, 62, 66, and [69] 68, or variants thereof).

The paragraph beginning at line 3 of page 11 has been amended as follows:

In particularly preferred embodiments, the polynucleotide hybridizes specifically to telomerase sequences, wherein the telomerase sequences are selected from the group consisting of human, *Euplotes aediculatus*, *Oxytricha, Schizosaccharomyces*, and *Saccharomyces* telomerase sequences. In other preferred embodiments, the present invention provides polynucleotide sequences comprising the complement of nucleic acid sequences selected from the group consisting of SEQ ID NOS:55, 62, 66, and [69] 68, or variants thereof. In yet other preferred embodiments, the

present invention provides polynucleic acid sequences that hybridize under stringent conditions to at least one nucleic acid sequence selected from the group consisting of SEQ ID NO:55, 62, 66, and [69] 68. In a further embodiment, the polynucleotide sequence comprises a purified, synthetic nucleotide sequence having a length of about ten to thirty nucleotides.

The paragraph beginning at line 15 of page 11 has been amended as follows:

In alternative preferred embodiments, the present invention provides polynucleotide sequences corresponding to the human telomerase, including SEQ ID NOS:[113 and 117] 173, 224, and their complementary sequences. The invention further contemplates fragments of these polynucleotide sequence (*i.e.*, SEQ ID NOS:[113, and 117] 173, 224) that are at least 5 nucleotides, at least 20 nucleotides, at least 100 nucleotides, at least 250 nucleotides, and at least 500 nucleotides in length. The invention further contemplates fragments of the complements of these polynucleotide sequences (*i.e.*, SEQ ID NOS:[113, and 117] 173, 224) that are at least 5 nucleotides, at least 20 nucleotides, at least 100 nucleotides, at least 250 nucleotides, and at least 500 nucleotides in length. In addition, the invention features polynucleotide sequences that hybridize under stringent conditions to SEQ ID NOS:[113 and 117] 173, 224, and/or fragments, and/or the complementary sequences thereof. The present invention further contemplates a polynucleotide sequence comprising the complement of the nucleic acids of SEQ ID NOS:[113 and 117] 173, 224, or variants thereof. In a further embodiment, the polynucleotide sequence comprises a purified, synthetic nucleotide sequence corresponding to a fragment of SEQ ID NOS:[113 and/or 117] 173, 224, having a length of about ten to thirty nucleotides. The present invention further provides plasmid pGRN121 (ATCC accession ##20916), and the lambda clone 25-1.1 (ATCC accession #____).

The paragraph beginning at line 3 of page 12 has been amended as follows:

The present invention further provides substantially purified polypeptides comprising the amino acid sequence comprising SEQ ID NOS:[114-116, and 118] 174-223, 225. In another embodiment, the present invention also provides purified, isolated polynucleotide sequences encoding the polypeptides comprising the amino acid sequences of SEQ ID NOS:[114-116, and 118] 174-223, 225. The present invention contemplates portions or fragments of SEQ ID NOS:[114-116, and 118] 174-223, 225, of various lengths. In one embodiment, the portion of polypeptide comprises fragments of lengths greater than 10 amino acids. However, the present invention also

contemplates polypeptide sequences of various lengths, the sequences of which are included within SEQ ID NOS:[114-116, and 118] 174-223, 225, ranging from 5 to 1100 amino acids (as appropriate, based on the length of SEQ ID NOS:[114-116, and 118] 174-223, 225).

The paragraph beginning at line 29 of page 12 has been amended as follows:

The present invention also provides antisense molecules comprising the nucleic acid sequence complementary to at least a portion of the polynucleotide of SEQ ID NO:55, 62, 66, 67, and [69] 68. In an alternatively preferred embodiment, the present invention also provides pharmaceutical compositions comprising antisense molecules of SEQ ID NOS:55, 62, 67, and [69] 68, and a pharmaceutically acceptable excipient and/or other compound (*e.g.,* adjuvant).

The paragraph beginning at line 9 of page 13 has been amended as follows:

The present invention also provides methods for producing polypeptides comprising the amino acid sequence of SEQ ID NOS:61, 63, 65, 67, or [69] 68, the method comprising the steps of: culturing a host cell under conditions suitable for the expression of the polypeptide; and recovering the polypeptide from the host cell culture.

The paragraph beginning at line 14 of page 13 has been amended as follows:

The present invention also provides purified antibodies that binds specifically to a polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NOS:55, [61,] 63, 64, 65, 67, and/or [68] 69. In one embodiment, the present invention provides a pharmaceutical composition comprising at least one antibody, and a pharmaceutically acceptable excipient.

The paragraph beginning at line 19 of page 13 has been amended as follows:

The present invention further provides methods for the detection of human telomerase in a biological sample comprising the steps of: providing a biological sample suspected of expressing human telomerase protein; and at least one antibody that binds specifically to at least a portion of the amino acid sequence of SEQ ID NOS:55, 61, 63, 64, 65, 67, and/or [68] 69; combining the biological sample and antibody(ies) under conditions such that an antibody:protein complex is formed; and detecting the complex wherein the presence of the complex correlates with the expression of the protein in the biological sample.

The paragraph beginning at line 27 of page 13 has been amended as follows:

The present invention further provides substantially purified peptides comprising the amino acid sequence selected from the group consisting of SEQ ID NOS:71, 73, 75, 77, 79, 82, 83, [83,] 85, [86,] and 101. In an alternative embodiment, the present invention provides purified, isolated polynucleotide sequences encoding the polypeptide corresponding to these sequences. In preferred embodiments, the polynucleotide hybridizes specifically to telomerase sequences, wherein the telomerase sequences are selected from the group consisting of human, *Euplotes aediculatus*, *Oxytricha, Schizosaccharomyces*, *Saccharomyces* and *Tetrahymena* telomerase sequences. In yet another embodiment, the polynucleotide sequence comprises the complement of a nucleic acid sequence selected from the group consisting of SEQ ID NOS:70, 72, 74, 76, 78, 80, 81, 100, [113, 117] 173, 224, and variants thereof. In a further embodiment, the polynucleotide sequence that hybridizes under stringent conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NOS:66, [69] 68, 80, and 81. In yet another embodiment, the polynucleotide sequence is selected from the group consisting of SEQ ID NOS:70, 72, 74, 76, 78, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, [113, and 117] 173 and 224. In an alternative embodiment, the nucleotide sequence comprises a purified, synthetic nucleotide sequence having a length of about ten to fifty nucleotides.

The paragraph beginning at line 15 of page 14 has been amended as follows:

The present invention also provides methods for detecting the presence of nucleotide sequences encoding at least a portion of human telomerase in a biological sample, comprising the steps of, providing: a biological sample suspected of containing nucleic acid corresponding to the nucleotide sequence of SEQ ID NO:100, and/or SEQ ID NO:[113] 173, and/or SEQ ID NO:[117] 224; the nucleotide of SEQ ID NO:100, and/or SEQ ID NO:[113] 173, and/or SEQ ID NO:[117] 224, or fragment(s) thereof; combining the biological sample with the nucleotide under conditions such that a hybridization complex is formed between the nucleic acid and the nucleotide; and detecting the hybridization complex.

The paragraph beginning at line 24 of page 14 has been amended as follows:

In one embodiment of the method the nucleic acid corresponding to the nucleotide sequence of SEQ ID NO:100, and/or SEQ ID NO:[113] 173, and/or SEQ ID NO:[117] 224, is ribonucleic acid, while in an alternative embodiment, the nucleotide sequence is deoxyribonucleic acid. In yet another embodiment of the method the detected hybridization complex correlates with expression of the polynucleotide of SEQ ID NO:100, and/or SEQ ID NO:[113] 173, and/or SEQ ID NO:[117] 224, in the biological sample. In yet another embodiment of the method, detection of the hybridization complex comprises conditions that permit the detection of alterations in the polynucleotide of SEQ ID NO:100 and/or SEQ ID NO:[113] 173, and/or SEQ ID NO:[117] 224, in the biological sample.

The paragraph beginning at line 4 of page 15 has been amended as follows:

The present invention also provides antisense molecules comprising the nucleic acid sequence complementary to at least a portion of the polynucleotide of SEQ ID NOS:82, 100, [113, and 117] 173 and 224. In an alternatively preferred embodiment, the present invention also provides pharmaceutical compositions comprising antisense molecules of SEQ ID NOS:82, 100, [113, 117] 173, 224, and a pharmaceutically acceptable excipient and/or other compound (*e.g.*, adjuvant).

The paragraph beginning at line 14 of page 15 has been amended as follows:

The present invention also provides methods for producing polypeptides comprising the amino acid sequence of SEQ ID NOS:82, 83, 84, 85, 86, 101, [114, 115, 116,] 174-223 and/or [118] 225, the method comprising the steps of: culturing a host cell under conditions suitable for the expression of the polypeptide; and recovering the polypeptide from the host cell culture.

The paragraph beginning at line 19 of page 15 has been amended as follows:

The present invention also provides purified antibodies that binds specifically to a polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NOS:71, 73, 75, 77, 79, 82, 83, 84, 85, [86,] 101, [114, 115, 116] 174-223, and/or [118] 225. In one embodiment, the present invention provides a pharmaceutical composition comprising at least one antibody, and a pharmaceutically acceptable excipient.

The paragraph beginning at line 24 of page 15 has been amended as follows:

The present invention further provides methods for the detection of human telomerase in a biological sample comprising the steps of: providing a biological sample suspected of expressing human telomerase protein; and at least one antibody that binds specifically to at least a portion of the amino acid sequence of SEQ ID NOS:71, 73, 75, 77, 79, 82, 83, 84, 85, [86,] 87, 101, [114, 115, 116] 174-223, and/or [118] 225, combining the biological sample and antibody(ies) under conditions such that an antibody:protein complex is formed; and detecting the complex wherein the presence of the complex correlates with the expression of the protein in the biological sample.

The paragraph beginning at line 27 of page 17 has been amended as follows:

Figure 25 shows the alignment of the human telomere amino acid motifs (SEQ ID NO:[61] 67), with portions of the tez1 sequence (SEQ ID NO:63), Est2p (SEQ ID NO:64), and the *Euplotes* p123 (SEQ ID NO:65).

The paragraph beginning at line 6 of page 18 has been amended as follows:

Figure 29 shows the amino acid sequence of *tez1* (SEQ ID NO:[68] 69).

The paragraph beginning at line 7 of page 18 has been amended as follows:

Figure 30 shows the DNA sequence of *tez1* (SEQ ID NO:[69] 68).

The paragraph beginning at line 12 of page 18 has been amended as follows:

Figure 34 (SEQ ID NOS:118-121) shows two degenerate primers used in PCR to identify the *S. pombe* homolog of the *E. aediculatus* p123 sequences.

The paragraph beginning at line 14 of page 18 has been amended as follows:

Figure 35 (SEQ ID NOS:119, 121) shows the four major bands produced in PCR using the degenerate primers.

The paragraph beginning at line 16 of page 18 has been amended as follows:

Figure 36 (SEQ ID NOS:58, 118, 121-130) shows the alignment of the M2 PCR product with *E. aediculatus* p123, *S. cerevisiae*, and *Oxytricha* telomerase protein sequences.

The paragraph beginning at line 18 of page 18 has been amended as follows:

Figure 37 (SEQ ID NOS:131-132) is a schematic showing the 3' RT PCR strategy.

The paragraph beginning at line 24 of page 18 has been amended as follows:

Figure 41 (SEQ ID NOS:133-147) shows the alignment of RT domains from telomerase catalytic subunits.

The paragraph beginning at line 26 of page 18 has been amended as follows:

Figure 42 (SEQ ID NOS:2, 55, 69) shows the alignment of three telomerase sequences.

The paragraph beginning at line 3 of page 19 has been amended as follows:

Figure 46 shows the DNA (SEQ ID NO:[69] 68) and amino acid (SEQ ID NO:[68] 69) sequence of *tez1*, with the coding regions indicated.

The paragraph beginning at line 8 of page 19 has been amended as follows:

Figure 48 (SEQ ID NOS:148-171) shows an alignment of reverse transcriptase motifs from various sources.

The paragraph beginning at line 11 of page 19 has been amended as follows:

Figure 50 provides the results of preliminary nucleic acid sequencing analysis of human telomerase (SEQ ID NO:[113] 173).

The paragraph beginning at line 13 of page 19 has been amended as follows:

Figure 51 provides the preliminary nucleic acid (SEQ ID NO:[113] 173) and deduced ORF sequences (SEQ ID NOS:[114-116] 174-223) of human telomerase.

The paragraph beginning at line 16 of page 19 has been amended as follows:

Figure 53 provides the nucleic acid (SEQ ID NO:[117] 224) and deduced ORF sequence (SEQ ID NO:[118] 225) of human telomerase.

The paragraph beginning at line 6 of page 34 has been amended as follows:

The present invention also provides nucleic and amino acid sequence information for human telomerase motifs. These sequences were first identified in a BLAST search conducted using the *Euplotes* 123 kDa peptide, and a homologous sequence from *Schizosaccharomyces*, designated as "tez1." Figure 25 shows the sequence alignment of the *Euplotes* ("p123"), *Schizosaccharomyces* ("tez1"), Est2p (*i.e.,* the *S. cerevisiae* protein encoded by the *Est2* nucleic acid sequence, and also referred to herein as "L8543.12"), and the human homolog identified in this comparison search. The amino acid sequence of this aligned portion is provided in SEQ ID NO:[61] 67 (the cDNA sequence is provided in SEQ ID NO:62), while the portion of tez1 shown in Figure 25 is provided in SEQ ID NO:63. The portion of Est2 shown in this Figure is also provided in SEQ ID NO:64, while the portion of p123 shown is also provided in SEQ ID NO:65.

The paragraph beginning at line 26 of page 34 has been amended as follows:

Figure 27 shows the amino acid sequence of the cDNA clone encoding human telomerase motifs (SEQ ID NO:67), while Figure 28 shows the DNA sequence of the clone. Figure 29 shows the amino acid sequence of tez1 (SEQ ID NO:[68] 69), while Figure 30 shows the DNA sequence of tez1 (SEQ ID NO:[69] 68). In Figure 30, the introns and other non-coding regions are shown in lower case, while the exons (*i.e.,* coding regions) are shown in upper case.

The paragraph beginning at line 18 of page 53 has been amended as follows:

Probes may also be used for the detection of related sequences and should preferably contain at least 50% of the nucleotides from any of these telomerase subunit protein sequences. The hybridization probes of the subject invention may be derived from the nucleotide sequence provided by the present invention (*e.g.,* SEQ ID NOS:1, 3, 62, 66, or [69] 68), or from genomic sequence including promoter, enhancer elements and introns of the naturally occurring sequence encoding telomerase subunit proteins. Hybridization probes may be labeled by a variety of reporter groups, including commercially available radionuclides such as ^{32}P or ^{35}S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

The paragraph beginning at line 16 of page 95 has been amended as follows:

Figure 25 shows the sequence alignment of the *Euplotes* ("p123"), *Schizosaccharomyces* ("tez1"), Est2p (*i.e.,* the *S. cerevisiae* protein encoded by the *Est2* nucleic acid sequence, and also

referred to herein as "L8543.12"), and the human homolog identified in this comparison search. The amino acid sequence of this aligned portion is provided in SEQ ID NO:[61] 67 (the cDNA sequence is provided in SEQ ID NO:62), while the portion of tez1 shown in Figure 25 is provided in SEQ ID NO:63. The portion of Est2 shown in this Figure is also provided in SEQ ID NO:64, while the portion of p123 shown is also provided in SEQ ID NO:65. Figure 29 shows the amino acid sequence of tez1 (SEQ ID NO:[68] 69), while Figure 30 shows the DNA sequence of *tez1* (SEQ ID NO:[69] 68). In Figure 30, the introns and other non-coding regions, are shown in lower case, while the exons (*i.e.,* coding regions) are shown in upper case.

The paragraph beginning at line 22 of page 98 has been amended as follows:

The cDNA insert of plasmid pGRN121 was sequenced using techniques known in the art. Figure 49 provides a restriction site and function map of plasmid pGRN121 identified based on this preliminary work. The results of this preliminary sequence analysis are shown in Figure 50. From this analysis, and as shown in Figure 49, a putative start site for the coding region was identified at approximately 50 nucleotides from the *Eco*RI site (located at position 707), and the location of the telomerase-specific motifs, "FFYVTE" (SEQ ID NO:112), "PKP," "AYD," "QG", and "DD," were identified, in addition to a putative stop site at nucleotide #3571 (*See,* Figure 51). Figure 51 shows the DNA and corresponding amino acid sequences for the open reading frames in the sequence ("a" [SEQ ID [NO:114] NOS:174-201], "b" [SEQ ID [NO:115] NOS:202-214], and "c" [SEQ ID [NO:116] NOS:215-223]). However, due to the preliminary nature of the early sequencing work, the reading frames for the various motifs were found not to be in alignment.

The paragraph beginning at line 14 of page 99 has been amended as follows:

Further sequence analysis resolved the cDNA sequence of pGRN121, to provide a contiguous open reading frame that encodes a protein of molecular weight of approximately 127,000 daltons, and 1132 amino acids as shown in Figure 53 (SEQ ID NOS:[117 and 118] 224-225). A refined map of pGRN121 based on this analysis, is provided in Figure 52.